[CONTRIBUTION FROM THE MCPHERSON CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

Synthesis of the Six Carboxybenzo[c]phenanthrenes[1,2]

MELVIN S. NEWMAN AND HERBERT BODEN

Received September 26, 1960

1-Carboxybenzo[c]phenanthrene has been synthesized by carbonation of the corresponding lithium derivative prepared from 1-bromobenzo[c]phenanthrene by treatment with butyllithium. The other five carboxybenzo[c]phenanthrenes have been prepared by oxidation of the corresponding methyl groups by heating with aqueous sodium dichromate at 250°.

The reasons for the synthesis of the six carboxybenzo[*c*]phenanthrenes have been stated.[3] In this paper the syntheses are described.

The 2-, 3-, 4-, 5-, and 6-carboxy compounds were prepared by oxidation of the corresponding methylbenzo[*c*]phenanthrenes with aqueous sodium dichromate[4] at 250°. This method of oxidation is noteworthy because a nucleus sensitive to other oxidizing agent is not attacked—rather, the methyl groups are. Oxidation of 1-methylbenzo[*c*]phenanthrene under these conditions yielded mainly 1,8,9-naphthanthr-10-one[5] but no acidic product. The desired 1-carboxybenzo[*c*]phenanthrene was prepared from 1-bromobenzo[*c*]phenanthrene[6] by treatment with butyllithium followed by carbonation. We were unable to prepare a Grignard reagent from the 1-bromo compound, even in tetrahydrofuran. Attempts at hydrolysis of 1-cyanobenzo[*c*]phenanthrene[6] under acidic conditions yielded either unchanged nitrile or 1,8,9-naphthanthr-10-one whereas under alkaline conditions the amide was obtained.

6-Carboxybenzo[*c*]phenanthrene was also prepared as before[7] from 1-bromo-2-naphthylacetic acid for which an improved (more rapid) preparation involving direct bromination of 2-naphthylacetic acid was used.

The samples of 2-methyl-, 3-methyl-, 4-methyl-, and 5-methylbenzo[*c*]phenanthrenes oxidized were those previously prepared.[8] The 1-methyl[9] and 6-methyl[7] isomers used were prepared by improvements of the previously described syntheses. The improvement in the synthesis of 1-methylbenzo[*c*]phenanthrene was centered mainly in the bishomologation of 2-methylbenzhydryl malonic acid to β-(2-methylbenzhydryl)glutaric acid.[10]

EXPERIMENTAL[11]

2-(o-Methylbenzhydryl)-1,3-propanediol. To a stirred suspension of 76 g. of lithium aluminum hydride in 2 l. of dry ether was added dropwise during 2 hr. a solution of 328 g. of diethyl *o*-methylbenzhydrylmalonate[12] in 500 ml. of ether. After refluxing for 4 hr. the mixture was poured on 2.5 l. of ice and 20% sulfuric acid. After the usual work up 238 g. (96.5%) of colorless diol, m.p. 102.5–105.0°, was obtained. The analytical sample, m.p. 105.8–106.8°, was obtained by recrystallization from carbon tetrachloride.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.7; H, 7.9. Found: C, 79.5; H, 7.8.

2-(o-Methylbenzhydryl)-1,3-propanediol bismethanesulfonate. A solution of 236 g. of the above diol, m.p. 102–105°, in 900 ml. of pyridine (dried over barium oxide) was converted into 376 g. (99%) of the crude bismethanesulfonate, m.p. 130–135°, as described for a similar case.[10] Recrystallization from absolute ethanol yielded the analytical sample, m.p. 132.4–134.0°, with little loss.

Anal. Calcd. for $C_{19}H_{24}O_6S_2$: C, 55.3; H, 5.9; S, 15.5. Found: C, 55.2; H, 6.0; S, 15.3.

β-(o-Methylbenzhydryl)glutaric acid. The entire bismethanesulfonate was converted into the dinitrile and the latter was hydrolyzed to the glutaric acid just as described for a similar conversion.[10] The yield of acid,[9] m.p. 201–204°, was 90%. The over-all yield from diethyl *o*-methylbenzhydrylmalonate to this point was 82%.

(1) This work was supported by grants G-2757 and G-9482 from the National Science Foundation.

(2) More details of the work reported herein may be found in the Ph.D. thesis presented by H. Boden to The Ohio State University, 1960.

(3) M. S. Newman and H. Boden, *J. Am. Chem. Soc.*, **83**, 115 (1961).

(4) This method of oxidation was used to convert toluene to benzoic acid, see German Patent **537,982**. Further applications of this method have been made by J. Ogilvie and R. S. Wilder, U. S. Patent **2,379,032** (1945), and by J. Ogilvie and A. J. Sweet, U. S. Patent **2,415,147** (1947), and by L. Friedman, Ph.D. thesis, Ohio State University, 1959. The latter showed that excellent yields of acids could be obtained from methyl derivatives of polycyclic hydrocarbons. See also L. Friedman, D. L. Fishel, and H. Shechter, Abstracts of papers presented at the 136th Meeting of the American Chemical Society, Atlantic City, N. J., 1959, p. 22P.

(5) See W. Bradley and F. K. Sutcliffe, *J. Chem. Soc.*, 2118 (1951) and references therein.

(6) M. S. Newman and D. K. Phillips, *J. Am. Chem. Soc.*, **81**, 3667 (1959).

(7) C. L. Hewett, *J. Chem. Soc.*, 1286 (1938). M. S. Newman and A. I. Kosak, *J. Org. Chem.*, **14**, 375 (1949).

(8) M. S. Newman, H. V. Anderson, and K. H. Takemura, *J. Am. Chem. Soc.*, **75**, 347 (1953).

(9) M. S. Newman and M. Wolf, *J. Am. Chem. Soc.*, **74**, 3225 (1952).

(10) See M. S. Newman and R. M. Wise, *J. Am. Chem. Soc.*, **78**, 450 (1956) for improvement in an analogous case.

(11) The term worked up in the usual way means that a solution of the product in question was washed with alkali and/or acid (as indicated) and with saturated salt solution. The solution was then filtered through a filter paper containing powdered anhydrous magnesium sulfate and the solvents were then distilled from the filtrate. Melting points are uncorrected unless otherwise noted. Microanalyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Skellysolves F, B, and C are petroleum ether fractions boiling in the ranges 35–55°, 65–69° and 90–97° respectively.

(12) This ester was prepared by Dr. H. V. Anderson, see Ref. (8).

5,6,6a,7,8,12b-Hexahydro-1-methylbenzo[c]phenanthrene-5 8-dione. In the best of several runs 30.0 g. of the above finely powdered glutaric acid was stirred into 600 g. of hot polyphosphoric acid[13] and the stirred mixture was held at 135–145° for 70 min., during which time the color changed from colorless to olive green. The mixture was poured on 2 kg. of ice. After standing in the ice box overnight the tan solid was filtered and dissolved in ether-benzene. After an alkaline wash the solvents were removed and the product crystallized from alcohol to yield 23.6 g. (89%) of dione, m.p. 180–182°. This yield is over twice that obtained by cyclization of the acid chloride.[9] When the time of heating was 55 min. and the temperature, 130–135°, the yield of dione was 80–81%.

1-Methylbenzo[c]phenanthrene. The above diketone (172.5 g.), aluminum isopropoxide (212 g.) and 1200 ml. of anhydrous isopropyl alcohol[14] were heated at reflux under a column until the distillate gave no further test with 2,4-dinitrophenylhydrazine reagent. After then distilling 400 ml. of isopropyl alcohol the mixture was worked up to yield 174 g. of diol, m.p. 120–135° (negligible carbonyl absorption in infrared). Crystallization of a portion from chloroform raised the m.p. to 135–145° but no analyses were run on the mixture of diols present. For further work, the mixture, m.p. 120–135°, was used.

In the best of several methods tried,[6] a solution of 40 g. of diol in 450 ml. of xylene containing 176 mg. of iodine was refluxed into a phase separating head for 3 hr., water being removed as formed. An additional 80 mg. of iodine was added and refluxing continued for 72 hr. (after 48 hr. no more water was being formed). The cooled solution was washed with sodium bisulfite and treated in the usual way. The light brown oil was chromatographed over alumina using combinations of benzene and Skellysolve B for elution. There was obtained 13.7 g. (39.5%) of 1-methylbenzo[c]phenanthrene, m.p. 138–140°, and 15.4 g. of a viscous tan oil. The latter was heated with 2.0 g. of sulfur at 225–235° for 1 hr. and treated as described below to yield 5.3 g. of hydrocarbon, m.p. 137.5–140.0°. Thus a total of 19.0 g. (55%) of aromatic hydrocarbon, was obtained.

A more rapid, but slightly lower yielding, process involved heating a mixture of 10.0 g. of diol and 1.15 g. of sulfur to 180° until dehydration appeared complete (about 1 hr.) and then heating at 225–235° for 1 hr. About 1 g. of zinc dust was added and the mixture was vacuum distilled to yield 4.27 g. of a light yellow oil which soon crystallized. Recrystallization from Skellysolve B afforded 3.84 g. (44%) of 1-methylbenzo[c]phenanthrene,[15] m.p. 138–140°.

Ethyl β-hydroxy-β-methyl-γ-phenylbutyrate. About 30 ml. of a solution of 376 g. (2.25 mole) of ethyl bromoacetate and 252 g. (1.88 moles) of phenylacetone[16] in 1350 ml. of dry thiophene-free benzene was added to 150 g. of 20 mesh granulated zinc in a flask equipped with a stirrer, reflux condenser and dropping funnel. After heating initiated reaction the remaining reagents were added at a rate sufficient to maintain moderate reflux. After the addition was complete (90 min.) the mixture was held at reflux for 2 hr. and worked up as usual.[11] Distillation afforded 370 g. (88%) of a light yellow oil, b.p. 121–135° at 1–2 mm., which was pure enough for a subsequent step.[17]

Ethyl β-methyl-γ-phenylcrotonate. To an ice-cold stirred solution of 222 g. of the above hydroxy ester in 158 g. of dry pyridine was added 238 g. of purified thionyl chloride[18] during 1 hr. After warming to room temperature during 1 hr., the reaction mixture was worked up as usual to yield a crude material to which was added about 20 g. of activated zinc dust.[19] Distillation afforded 196 g. (84.5% over-all from phenylacetone) of ethyl β-methyl-γ-phenylcrotonate, b.p. 89–91° at 0.5 mm. n_D^{20} 1.5168.

6-Methylbenzo[c]phenanthrene. Conversion of the above unsaturated compound to the final hydrocarbon was effected as described,[8] except that the cyclization of β-methyl-γ-phenylbutyric acid to 3-methyl-1-tetralone went in 93% yield.

1-Bromo-2-naphthylacetic acid. To a stirred solution of 150 g. of 2-naphthylacetic acid[20] in 500 ml. of glacial acetic acid and 400 ml. of carbon tetrachloride at 40° was added during 6 hr. 128 g. of bromine. The solution was held at 40° until the color was pale orange-yellow. After concentration to 300 ml. under reduced pressure filtration yielded 61.4 g. (29%) of crude acid, m.p. 190–192°. Recrystallization from 700 ml. of carbon tetrachloride afforded 57.7 g. (27%) of 1-bromo-2-naphthylacetic acid, m.p. 194.5–196.0°, which showed no depression when mixed with an authentic sample.[7,21]

6-Carboxybenzo[c]phenanthrene. The sodium salt of the above acid was condensed with benzaldehyde essentially as described[21] to yield pure α-(1-bromo-2-naphthyl)-β-phenylacrylic acid, m.p. 205.0–206.5°, in 66% yield. The remaining steps to 6-carboxybenzo[c]phenanthrene, m.p. 241–243,° followed the described procedures closely.[7]

1-Carboxybenzo[c]phenanthrene. To a stirred solution of 5.0 g. (0.016 mole) of 1-bromobenzo[c]phenanthrene,[6] in 350 ml. of dry ether under nitrogen was added dropwise a solution of 0.032 mole of *n*-butyllithium[22] in 80 ml. of ether. After stirring for 75 min. the solution was forced by nitrogen on to a suspension of solid carbon dioxide and ether. After the

TABLE I

CARBOXYBENZO[c]PHENANTHRENES AND METHYL ESTERS

Position	Yield, %	M.P.[a]	Found[b] Carbon, %	Found[b] Hydrogen, %
1	67[c]	251.5–253.0	83.7	4.6
1 ester[d]		116.5–117.5	83.8	4.8
2	64	221.0–222.0	83.9	4.6
2 ester		80.8–81.8	84.1	5.0
3	59	233.0–234.0	83.9	4.5
3 ester		130.2–130.8	83.9	4.8
4	71	250.0–251.0	83.8	4.5
4 ester		82.8–83.6	84.1	5.0
5	81	235.0–236.0	83.8	4.4
5 ester[e]		71.8–72.6	83.9	4.8
6	65	242.0–243.0	83.9	4.4
6 ester		98.0–99.0	83.8	4.8

[a] Melting points for acids determined on a Fisher hot stage melting point apparatus. [b] Calcd. for acids, $C_{19}H_{12}O_2$: C, 83.8; H, 4.4. Calcd. for methyl esters, $C_{20}H_{14}O_2$: C, 83.9; H, 4.9. [c] Yield for 1-isomer from carbonation of lithium derivative [all other yields for oxidation of methyl groups]. [d] Methyl esters. [e] A m.p. of 76–77° has been reported by C. L. Hewett, *J. Chem. Soc.*, 293 (1940). Our form is a polymorphic form.

(13) We thank the Victor Chemical Co., Chicago, Ill., for a generous sample of polyphosphoric acid.

(14) Compare A. L. Wilds, *Org. Reactions*, 198 (1944).

(15) M. S. Newman and W. B. Wheatley, *J. Am. Chem. Soc.*, **70**, 1913 (1948), report a m.p. of 141.4–141.9° corr., for pure hydrocarbon. The identity with the present sample was confirmed by mixed m.p. determination.

(16) Benzol Products Co., Newark 5, N. J.

(17) F. Weygand and K. Schroeder, *Ber.*, **74**, 1844 (1941) obtained a 79% yield. See also ref. 8 this paper.

(18) L. F. Fieser and E. L. Martin, *Org. Syntheses*, Coll. Vol. II, 570 (1943).

(19) Residual sulfur compounds poison the catalyst in the subsequent catalytic hydrogenation unless this zinc dust addition is made. The zinc is activated by treating with ammonium chloride solution, followed by washing successively with water, acetone, and ether, and drying.

(20) M. S. Newman, *J. Org. Chem.*, **9**, 518 (1944).

(21) F. Mayer and A. Sieglitz, *Ber.*, **55**, 1858 (1922) reported a m.p. of 194°.

(22) H. Gilman *et al.*, *J. Am. Chem Soc.*, **71**, 1499 (1949).

usual workup 2.95 g. (67%) of yellow acid, m.p. 247–250°, was obtained. Recrystallization from aqueous alcohol yielded (61%) of pale yellow 1-carboxybenzo[c]phenanthrene, m.p. 249.5–251.5°. From the neutral portion of the reaction products there was obtained 0.48 g. of benzo[c]phenanthrene.

Oxidation of methylbenzo[c]phenanthrenes. In a typical case, a mixture of 3.00 g. of 2-methylbenzo[c]phenanthrene, m.p. 79.6–81.0°, 5.50 g. of sodium dichromate dihydrate, and 100 ml. of water was enclosed in 450-ml. stainless steel bomb. The bomb was rocked and heated at 250° for 65 hr. On suitable workup of the contents 2.48 g. (74%) of yellow acid, m.p. 214–221°, and 0.56 g. (19%) of 2-methylbenzo-[c]phenanthrene, m.p. 78–80°, were obtained. Recrystallization of the crude acid from toluene afforded 2.15 g. (64%) of pale yellow 2-carboxybenzo[c]phenanthrene, m.p. 220–222°. 3-, 4-, 5-, and 6-methylbenzo[c]phenanthrene were oxidized similarly. These oxidations are remarkably clean as the crude reaction products are not deeply discolored and the recovery of pure acid and starting hydrocarbon is in the 85–95% region in most runs. The yields and properties of the acids are listed in Table I.

When the 1-methyl isomer was treated similarly for 15 hr., 0.62 g. (31%) was recovered and 0.97 g. (46%) of 1,8,9-naphthanthr-10-one,[5] m.p. 240–242°. The mixed m.p. with an authentic sample was not depressed. We were unsuccessful in attempts to prepare a 2,4-dinitrophenylhydrazone or an oxime from this ketone. The 1-acid dissolved in concentrated sulfuric acid to produce a deep red color. On pouring this solution into water 1,8,9-naphthanthr-10-one was formed.

The methyl esters were prepared from 2-, 3-, 4-, 5-, and 6-carboxybenzo[c]phenanthrene by acid-catalyzed esterification. Since the rate of esterification of the 1-isomer was very slow this ester was prepared with diazomethane. The properties of the methyl esters are listed in Table I.

COLUMBUS 10, OHIO

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE & CO.]

Tricyclic Naphthalenic Steroid Analogs

DOUGLAS S. SMITH[1] AND KURT RORIG

Received September 28, 1960

1-Acetyl-3-(6-methoxy-2-naphthyl)cyclohexane (IV), 1-acetoxyacetyl-3-(6-methoxy-2-naphthyl)cyclohexane (VI), and 1-acetyl-3-(6-hydroxy-2-naphthyl)cyclohexane (VII) have been prepared from 3-(6-methoxy-2-naphthyl)cyclohexanone.

Recently in the steroid field a great deal of interest has been evidenced in modifications of the naturally occurring substances and also in the preparation of synthetic analogs bearing a formal structural relationship to the cortical hormones. In an attempt to delineate the limits within which steroid activity might be found as well as to keep the synthetic and stereo-chemical problems to a minimum, we have prepared a series of naphthyl substituted cyclohexane derivatives oxygenated in such positions as formally to resemble some steroid molecules lacking the complete elements of ring C.

The starting material for our syntheses, 3-(6-methoxy-2-naphthyl)cyclohexanone, has been described by Novello and Christy.[2] However, our preparation of the immediate precursor of this compound, 3 - (6 - methoxy - 2 - naphthyl) - 2 - cyclohexen-1-one (I), differed from that reported.[2] Thus, in a simpler and more direct synthesis, treatment of the ethyl ether of dihydroresorcinol[3] with 6 - methoxy - 2 - naphthylmagnesium bromide gave a 46% yield of I. Whether the Grignard reagent adds normally to the ketone followed by hydrolysis of the enol ether and dehydration to give I, or whether addition takes place in the conjugate 1,4-manner followed by elimination of the elements of ethanol is uncertain since the same product results in either case. The 3-(6-methoxy-2-naphthyl)cyclohexanone was converted to its cyanohydrin (II), which was dehydrated with pyridine and phosphorus oxychloride to give 1-cyano - 3 - (6 - methoxy - 2 - naphthyl)cyclohexene (III), probably as a mixture of double bond isomers. Reduction in the presence of palladium-on-carbon, followed by treatment with methylmagnesium bromide and subsequent hydrolysis of the intermediate imine gave 1-acetyl-3-(6-methoxy-2-naphthyl)cyclohexane (IV), obtained in 57% over-all yield from the starting ketone. Compound IV existed in two polymorphic forms, but apparently was a pure racemate, and is therefore thought to be the *cis* isomer (the most stable form, with both substituents on the cyclohexane ring in equatorial positions).

Demethylation of IV with pyridine hydrochloride gave a 52–58% yield of 1-acetyl-3-(6-hydroxy-2-naphthyl) cyclohexane (VII), obtained as a mixture of racemates.

1 - Hydroxy - 3 - (6 - methoxy - 2 - naphthyl)-1-cyclohexanecarboxylic acid (V) was considered to be a likely intermediate for the preparation of analogs containing the "dihydroxyacetone" side chain of cortisone. Accordingly the cyanohydrin II was hydrolyzed with hydrochloric acid to give V, but the yield was so poor that this route was abandoned.

Compound IV was allowed to react with ethyl oxalate in the presence of sodium methoxide and the sodium enolate of the condensation product was treated with iodine to yield crude 1-iodoacetyl-3-

(1) Vick Chemical Co., Greensboro, N. C.

(2) F. C. Novello and M. E. Christy, *J. Am. Chem. Soc.*, **75**, 5431 (1953).

(3) G. F. Woods and I. W. Tucker, *J. Am. Chem. Soc.*, **70**, 2174 (1948).